REMARKS

Favorable consideration and allowance are respectfully requested for claims 17 and 38 in view of the following remarks.

To perfect the previously submitted claim of priority, an certified English translation of the priority document is submitted herewith.

The rejection of claim 17 under 35 U.S.C. § 102(b) over Mauskop (U.S. 5,914,129) is respectfully traversed.

The presently claimed formulation is a sustained release formulation comprising a compound formed *in situ* of tramadol hydrochloride and diclofenac sodium. The compound has a water solubility of ≤ 100 mg/ml and at least part of the tramadol and at least part of the diclofenac are released at the same rate.

The sustained release of the active substances tramadol and diclofenac is achieved by the *in situ* formulation of the compound. The *in situ* formulation of the compound is specifically outlined in the specification, for instance in the following paragraphs:

> **[0011]** To prepare the compound formed in situ, the active substance tramadol, preferably as a water-soluble salt and particularly preferably as tramadol hydrochloride, is reacted with a water-soluble, pharmaceutically acceptable salt of another, acidic pharmaceutical active substance or auxiliary substance which forms with tramadol a compound with a water solubility of ≤100 mg/ml, preferably ≤50 mg/ml, particularly preferably ≤30 mg/ml and very particularly preferably ≤10 mg/ml. These compounds are classified as sparingly water-soluble compounds.
>
> **[0012]** In the context of this specification, in situ formation means that the tramadol or a water-soluble salt thereof is mixed with another, acidic pharmaceutical active substance or auxiliary substance or water-soluble salts thereof, preferably during the preparation of the

> pharmaceutical formulation according to the invention, moistened several times and optionally extruded or formulated energy input.
>
> **[0013]** As the water-soluble salt of the other, acidic pharmaceutical active substance and/or biocompatible auxiliary substance for the preparation of the tramadol compound formed in situ, the sodium salt of diclofenac, naproxen, acetylsalicylic acid, salicylic acid, benzoic acid, saccharin, cyclamate or acesulfame is preferably used.

Paragraphs 17, 18 and 21 of the specification also relate to the *in situ* formation of certain embodiments of the compound. As can be appreciated from these paragraphs, and the disclosure in general, the *in situ* formation of the compound affects the water solubility characteristics of the compound. In this way, the *in situ*-formed compound causes the oral pharmaceutical form of administration to be at least partially sustained release. Additionally, in certain embodiments, tramadol release is at least partially retarded (depending on the amount of acidic substance being present during the preparation of the administrative form) by the *in situ* formation of a compound of tramadol and another active substance, without the use of a sustained release matrix and/or a sustained release coating.

Further, at least part of the active substance tramadol and at least part of the diclofenac are released at the same rate. This requirement is not met by a compound wherein tramadol hydrochloride and diclofenac sodium are separate compounds within a composition.

Mauskop relates to a composition with a non-opioid analgesic agent and an opioid analgesic agent. The non-opioid analgesic agent may be diclofenac and the opioid analgesic agent may be tramadol. Mauskop does not teach or suggest a compound of tramadol hydrochloride and diclofenac sodium. Further, Mauskop certainly does not teach or suggest *in situ* formation of such a compound. Mauskop also does not teach or suggest a compound of tramadol hydrochloride

and diclofenac sodium where at least part of the tramadol and at least part of the diclofenac are released at the same rate. Moreover, Mauskop does not teach or suggest a compound of tramadol hydrochloride and diclofenac sodium with a solubility of ≤ 100 mg/ml. All of these are requirements of presently pending claim 17.

In order to anticipate a claim, a reference must teach each and every element of that claim. As set forth above, Mauskop fails to teach several elements of claim 17, the lack of any one of which renders the rejection improper. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) are respectfully requested.

The rejection of claim 38 under 35 U.S.C. § 103 over Mauskop (U.S. 5,914,129) in view of Remington's Pharmaceutical Sciences (1990) is respectfully traversed. In a telephonic conversation with Christopher McWhinney on March 22, 2004, Examiner Fubara confirmed that this rejection, in paragraph 11 of the Office Action, was maintained.

Claim 38 relates to a method for preparing a pharmaceutical formulation by mixing tramadol hydrochloride and diclofenac sodium to form a mixture; moistening the mixture; and repeating the mixing and moistening steps and formulating the mixture under an energy input.

The Office Action asserts that Mauskop does not teach the preparation of the composition as recited in claim 38, but that it would have been obvious to one of ordinary skill in the art to employ the granulation methods taught in Remington's Pharmaceutical Sciences to formulate a preparation. The Office Action provides no indication as to how the methods taught in Remington's Pharmaceutical Sciences could be used to arrive at a method comparable to the method of claim 38 of the present invention. Though not the same as the presently claimed method, Remington's wet granulation method appears to be

the most closely related to the method of claim 38. A person of ordinary skill in the art, however, would not be inclined to use wet granulation as the first option for preparing a pharmaceutical composition. Wet granulation is primarily used in the event of formulation problems, for instance overcoming undesirable rheological properties by adding lubricants. The references do not provide any teaching, suggestion, or other motivation to a person of skill in the art to try to combine the separate teachings of the two references. Since methods for preparing pharmaceutical formulations similar to that contemplated by the present invention are already known, one of skill in the art would not be inclined to try a more expensive and time consuming method of preparation, such as wet granulation. In this way, a person of skill in the art would actually be discouraged from trying a wet granulation method of preparation for a composition such as that presently contemplated.

Further, even if one were inclined to use wet granulation as a preparation method, a person of skill in the art would not be inclined to repeat the step of moistening the formulation several times during the preparation. A person of skill in the art would perceive these added steps as merely increasing the preparation costs, without any added return. Moreover, wet granulation with several moistening steps is not disclosed in the Remington's Pharmaceutical Sciences cited by the Examiner. Consequently, even assuming, *arguendo*, one were to combine the teachings of Mauskop with those of Remington's Pharmaceutical Sciences, the presently claimed method is not obtained. Further, one of skill in the art would have no motivation to modify the method resulting from the combination of Mauskop and Remington's Pharmaceutical Sciences so as to arrive at the presently claimed method.

Thus, because there is no motivation to combine the references, and because even if they were combined they do not teach each and every element of the claimed method, and because there is no motivation to modify the combined

teachings of the references, the cited combination does not render claim 38 obvious. Accordingly, reconsideration and withdrawal of the obviousness rejection are respectfully requested.

Claim 17 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and and 11 of co-pending Application no. 10/016,130. Claim 17 of the present application is patentably distinct from the claims of co-pending Application no. 10/016,130. A basic requirement of the various embodiments of the present application is that tramadol and diclofenac and/or their respective physiologically compatible salts are formulated together *in situ* as a compound to arrive at a resulting compound having a low water solubility. In contrast thereto, a basic requirement of the embodiments of Application no. 10/016,130 is that tramadol and diclofenac and/or their respective physiologically compatible salts are present in separate subunits which are each separately formulated. Further, co-pending Application no. 10/016,130 teaches a separation layer between the two separately formulated sub-units in order to avoid any contact between the two active substances. Because the co-pending application requires separate formation of the two active substances, and the present application requires formation of the two active substances together into a compound, the claims are patentably distinct. Accordingly, the subject matter of the present claims is not obvious in view of the claims of the earlier application and withdrawal of the provisional obviousness-type double-patenting rejection is respectfully requested.

CONCLUSION

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

Although a petition for an Extension of Time is submitted herewith, if necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket No. 029310.50932).

Respectfully submitted,

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